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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HIBBERT, CATHERINE S	

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
09/16/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/594,851	CHENEVAL ET AL.	
	Examiner	Art Unit	
	Catherine Hibbert	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/24/2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *10-13,18 and 23-39* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *10-13,18 and 23-39* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/24/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's Amendment to the Specification, Amendment to the Claims, and Supplemental Application Data Sheet, all filed 6/24/2011, are received and entered.

Claims 10-13, 18 and 23-39 are pending and under examination.

Priority

Current claims 10-13, 18 and 23-39 receive priority to 4/1/2004 the filing date of the parent application 10/814,634.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 6/24/2011 has been considered by the examiner.

Response to Amendments/Arguments

The objection to the specification is withdrawn based on the Amendment to the Specification filed 6/24/2011.

The rejection of claims 23-25 and 35-36 under 35 U.S.C. 112, second paragraph, is WITHDRAWN based on claim amendments filed 6/24/2011.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 10-13, 18 and 23-39 STAND rejected under 35 U.S.C. 103(a) as being unpatentable over Zubiaga et al. (1995, MCB, Vol 15, No.4, pages 2219-2230; of record in the IDS), in view of Banholzer et al (Molecular Cellular Biology, 1997, Vol 17, No.6, pages 3254-3260; of record in the IDS), in view of Lemm and Ross (Molecular and Cellular Biology, 2002, Vol 22, No. 12, pages 3959-3969; of record in the IDS). It is noted that claim 18 was included in the body of the rejection in the previous office action but was inadvertently omitted from the first line of the rejection.

Claims 10-13, and 23-31 are drawn to a method of screening for one or more compound which affect mRNA stability comprising the steps of:

i) contacting a DNA expression system with at least one test compound under conditions whereby, in the absence of the test compound, said DNA expression system expresses a protein having a detectable signal, wherein the mRNA which is transcribed from said expression system and encodes said protein comprises at least one copy of a heterologous mRNA instability sequence comprising one or more coding region determinant (CRD) or a fragment thereof;

(ii) measuring said detectable signal; and

(iii) comparing the measured detectable signal with a control, wherein a decrease in the measured detectable signal compared to said control indicates a compound that decreases mRNA stability and an increase in the measured detectable signal compared to said control indicates a compound that increases mRNA stability.

Claim 11 specifies that the control comprises measuring the detectable signal from the DNA expression system in the absence of the test compound. Claim 12 specifies that the control comprises contacting a control expression system capable of expressing a second protein having a second detectable signal with the test compound and measuring said second detectable signal. Claim 13 specifies that the compounds are being screened for their ability to induce mRNA degradation, and wherein a decrease in the measured detectable signal compared to said control indicates a compound that induces mRNA degradation. Claim 26 specifies that the heterologous mRNA instability sequence is inserted into the 3'UTR of the gene encoding the protein having a detectable signal. Claims 23 /24/25 specify that the heterologous mRNA instability sequence is from a naturally occurring source gene/encoding a protein implicated in a disease of interest/c-myc. Claim 27 specifies within claim 23, that the heterologous mRNA instability sequence further comprises DNA corresponding to the regions that flank said CRD or fragment thereof in the naturally occurring source gene or mRNA. Claim 28 specifies within claim 27 that the heterologous mRNA instability sequence is inserted into the 3'UTR of the gene encoding the protein having a detectable signal. Claims 29/30/31 specify that the protein having a detectable signal is an enzyme/ luciferase or β-galactosidase/ is a fluorescent or phosphorescent protein.

Claims 18 and 32-39 are drawn to a high throughput method for screening libraries of compounds to identify compounds that affect the stability of mRNA comprising:

(i) inoculating wells of one or more multi-well plates comprising a growth medium with a stably transfected cell line comprising a DNA expression vector, which in the absence of a test compound expresses a protein having a detectable signal, wherein the mRNA which is transcribed from said expression vector and encodes said protein comprises at least one copy of a heterologous mRNA instability sequence comprising one or more coding region determinant (CRD) or a fragment thereof;

(ii) maintaining the one or more multi-well plates under conditions that allow cells of the cell line to grow and express the protein having a detectable signal;

(iii) contacting the cells with one or more test compound;

(iv) measuring the detectable signal; and

(v) comparing the measured detectable signal with a control; wherein a decrease in the measured detectable signal compared to the control indicates a compound that decreases mRNA stability and an increase in the measured detectable signal compared to the control indicates a compound that increases mRNA stability.

Claim 32 specifies that the control comprises measuring the detectable signal from the stably transfected cell line in the absence of said test compound. Claim 33 specifies that the stably transfected cell line comprises a second DNA expression vector capable of expressing a second protein having a second detectable signal, and wherein said control comprises measuring the second detectable signal. Claim 34 specifies that the compounds are being screened for their ability to induce mRNA degradation, and wherein a decrease in the measured detectable signal compared to said control indicates a compound that induces mRNA degradation. Claims 35/36 specify that the heterologous mRNA instability sequence is from a naturally occurring source

gene/ c-myc. Claim 37 specifies that the heterologous mRNA instability sequence is inserted into the 3'UTR of the gene encoding the protein having a detectable signal. Claim 38 specifies within claim 35, that the heterologous mRNA instability sequence further comprises DNA corresponding to the regions that flank the CRD or fragment thereof in the naturally occurring source gene or mRNA. Claim 39 specifies that the heterologous mRNA instability sequence is inserted into the 3'UTR of the gene encoding the protein having a detectable signal.

Zubiaga et al disclose an expression vector comprising c-fos promoter operatively linked to globin gene, wherein several ARE isolated from c-fos is inserted into 3'UTR of the globin gene (see page 2220, 2nd col., 6th paragraph), resulting in sets of cell lines comprising different expression constructs. Zubiaga et al also disclose that a control plasmid pRSV-lacZ, comprising a gene coding for expression of lacZ, 5' and 3' UTR for expression of said gene without mRNA instability sequence (see page 2221, 1st co1., 2nd paragraph, lines 4-9). Zubiaga et al further disclose that these construct are co-transfected into NIH-3T3 cells (see page 2221, 1st Col., 2nd paragraph, lines 1-4).

Banholzer et al disclose that rapamycin promotes degradation of IL-3 transcripts at posttranscriptional level via 3' UTR (see page 3257, 2nd col., 1st paragraph). Banholzer et a. disclose two cell lines stably transfected with IL-3 expression system either with (VD1-M1) or without (VD1-M1AAU) mRNA instability sequence (3' UTR) (see page 3256, 1st col., lines 1-3). Banholzer et al also disclose that following rapamycin and FK506 treatment, endogenous and exogenous wild type IL-3 decayed with very similar kinetics (see Figure 3b, left panel) whereas the exogenous mutant IL-3 mRNA level is not affected by either compound (Figure 3b,

right panel, and 3c). The method and assay system disclosed by Banholzer et al identifies rapamycin and FK506 as compounds that induce mRNA degradation.

While, Zubiaga et al do not teach an assay system for screening compounds which destabilize mRNA that comprises a stably transfected cell line as claimed and a test compound, it would have been obvious for one of ordinary skill in the art to develop such an assay system with the prior art of Banholzer et al before them because Banzolzer et al disclosed that one of ordinary skill in the art is able to screen compounds such as rapalogs for their ability to modulate the mRNA instability sequence. One of ordinary skill in the art would have been motivated to screen compounds that would affect ARE sequence instability using the heterologous expression construct as disclosed in Zubiaga et al for the rationale of distinguishing post-translational from post-transcriptional mRNA instability.

Further, one of ordinary skill in the art would also be motivated to use stably transfected cell lines for the rationale that they are easy to maintain such that one does not have to do transfection every time to test a compound.

The level of skill in the art is high. Absent evidence from the contrary, one of ordinary skilled in the art would have reasonable expectation of success to use the cell line taught by Zubiaga as a system to test compounds and make the cell line a stably transfected cell for said purpose.

While neither of the references of Zubiaga and Banholzer explicitly teach a coding region instability determinant as the instability sequence, this element is known in the prior art as shown in the reference of **Lemm and Ross.** Lemm and Ross teach a 249 nucleotide coding region from c-myc destabilizes c-myc mRNA. Lemm and Ross also teach that the nucleotide sequence

destabilizes beta-globin mRNA when inserted in frame within the coding region of said beta-globin gene (see page 3959, 2nd CO1., 2nd paragraph).

It would have been obvious to one of ordinary skill in the art to use the cell lines with constructs that have instability sequence as taught by either Zubiaga et al. or Banholzer et al. to test compounds that affect coding region instability determinants (CRD) from c-myc. One of ordinary skill in the art would have been motivated to do so for the rationale of ease of screening compounds that modulates the activity of the CRD. Absent evidence from the contrary, the ordinary artisan would have reasonable expectation of success to insert the CRD into a construct which can then be transfected into a cell line for testing compounds.

Response to Arguments

Applicants' arguments have been fully considered but are respectfully found unpersuasive. Applicants submit that "Zubiaga, Banholzer and/or Lemm and Ross alone or in combination, do not render claim 10 and its dependent claims obvious". Applicants' argue that "Claim 10 and its dependent claims are directed to methods of screening using a DNA expression system, wherein the mRNA which is transcribed from said expression system comprises at least one copy of a heterologous mRNA instability sequence comprising one or more coding region determinant (CRD) or fragment thereof". Applicants further argue:

> Zubiaga et al focuses on identifying the minimal AU-rich motif capable of destabilizing mRNA. Various constructs comprising different ARE sequences inserted into the 3'UTR of the β-globin gene were made and transiently transfected into NIH 3T3 cells. The stability of mRNA containing different sequences were evaluated and compared based on Northern blot analyses. As acknowledged by the Examiner, Zubiaga neither teaches an assay system for screening compounds which destabilize mRNA, nor teaches a coding region instability determinant as the instability sequence.

> Banholzer et al focuses on understanding the mechanisms by which rapamycin ("RAPA"), a known immunosuppressive drug, downregulates IL-3 mRNA in a tumor mast cell line. Genomic IL-3 wild-type sequences or a sequence lacking the AU-rich element (ARE) were transfected into separate tumor cell lines. The effects of rapamycin on the IL-3 mRNAs were evaluated. To determine whether the 3'UTR of IL-3 would confer sensitivity to a heterologous transcript, Banholzer et al also examined the effect of rapamycin on AP reporter constructs carrying the 3'UTR of IL-3 with or without deletion of the ARE.
>
> Furthermore, Banholzer concluded that "IL-3 3'UTR could confer RAPA sensitivity to reporter transcripts, provided that the 3'UTR sequence was intact." Banholzer thus conveys to a person of ordinary skill in the art that, for the purpose of studying the effect of rapamycin on IL-3 mRNA, it is important to keep the mRNA instability sequence in its natural state. As acknowledged by the Examiner, Banholzer does not teach a coding region instability determinant as the instability sequence.
>
> The Examiner relies on Lemm and Ross as allegedly teaching that a 249 nucleotide coding region from c-myc destabilizes c-myc and that such sequence destabilizes beta-globin mRNA when inserted in frame within the coding region of beta-globin. The Examiner thus concludes that "it would have been obvious to one of ordinary skill in the art to use the cell lines with constructs that have instability sequence as taught by either Zubiaga et al. or Banholzer et al. to test compounds that affect coding region instability determinants (CDR) from c-myc." Page 9 of Office Action.
>
> As discussed in Lemm and Ross, the coding region instability determinant (CRD) functions independently of the AU-rich element to make the mRNA instable. Page 3959, fight column, second paragraph. Lemm and Ross teach that the CRD "must be translated to destabilize the mRNA," and that "[p]lacing a translational stop codon upstream of the CRD stabilizes the chimeric RNA." Page 3959, right column, second paragraph. Lemm and Ross further discuss regulation of c-myc mRNA decay by "translational pausing" in the CRD. One of ordinary skill in the art reading Lemm and Ross would clearly understand that the CRD discussed therein has to be present in the coding region in order for "translational pausing" to occur, and that placing the CRD into the 3'UTR would be ineffective in destabilizing mRNA. This is also acknowledged by the Examiner, who states that the 249 nucleotide coding region from c-myc "destabilizes beta-globin mRNA when inserted in frame within the coding region of said beta-globin gene." Page 9 of Office Action.

Accordingly, Applicants submit that “Lemm and Ross not only provide no motivation but also teach away from inserting a CRD into an heterologous 3'UTR construct of Zubiaga, which is designed to identify the minimal AU rich sequence motif that destabilizes mRNA or from

inserting a CRD into the 3'UTR of IL-3 in a construct disclosed by Banholzer which is designed to test the effect of rapamycin on the 3'UTR of β-globin.

Applicants' arguments have been fully considered but are unpersuasive because in response to applicant's arguments, the recitation "a method of screening for one or more compound which affects mRNA stability" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao,* 535 F.2d 67, 190 USPQ 15 (CCPA 1976) *and Kropa v. Robie,* 187 F.2d 150, 152, 88 USPQ 478,481 (CCPA 1951). Banholzer teach "contacting a DNA expression system with rapamycin," wherein rapamycin affects mRNA stability in said system. Further, the specification does not specify what is considered to be a detectable signal. As such, detecting mRNA transcripts which codes for the protein (by means of Northern blotting) meets the limitation of measuring the detectable signal, wherein the signal shows up on the blot.

In response to applicant's argument that regarding the reference of Lemm and Ross, that one of ordinary skill in the art reading Lemm and Ross would clearly understand that the CRD discussed therein has to be present in the coding region in order for "translational pausing" to occur, and that placing the CRD into the 3'UTR would be ineffective in destabilizing mRNA, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must

be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

In regards to the applicant's argument that one of ordinary skill in the art would not be motivated to insert a CRD into an heterologous 3'UTR construct because the art teaches away from this step, the Examiner presents evidence herein in the reference of Davis et al in "A Coding Region Determinant of Instability Regulates Levels of Manganese Superoxide dismutase mRNA" (JBC: October, 2001 Vol. 276, No. 40 pages 37317-37326) to show that the art does not teach away from insertion into a heterologous 3'UTR. For example, Davis et al explicitly teach that one of ordinary skill in the art would be motivated to insert a CRD into a 3'UTR, stating in lines 17-21 of the abstract that "the MnSOD coding region determinant functions when placed in the 3'-untranslated region of the beta-globin transcript, demonstrating its activity in the absence of ribosome transit".

In view of the foregoing, the method of claims 10-13, 18 and 23-39, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC *§103(a).*

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10-13, 18 and 23-39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-14, 18, 23-25, 27-32, and 34-43 of copending Application No. 11/868,397 (US2009/068654. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims anticipate the instant claims except that the conflicting claims do not specify that the

heterologous mRNA instability sequence comprises a coding region determinant (CRD) or fragment thereof as required of the instant claims 10-13, 18 and 23-39.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. This is a new grounds of rejection prompted by the submission of an IDS.

Conclusion

No claims allowed.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 6/24/2011 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine Hibbert whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Catherine Hibbert
Examiner AU1636

/NANCY VOGEL/

Primary Examiner, Art Unit 1636